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Comparative pharmacokinetics of perfluorooctanesulfonate (PFOS) in rats, mice, and monkeys

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ABSTRACT

Perfluorooctanesulfonate (PFOS) has been found in biological samples in wildlife and humans. The geometric mean half-life of serum elimination of PFOS in humans has been estimated to be 4.8 years (95% CI, 4.0–5.8). A series of studies was undertaken to establish pharmacokinetic parameters for PFOS in rats, mice, and monkeys after single oral and/or IV administration of K^+PFOS. Animals were followed for up to 23 weeks, and pharmacokinetic parameters were determined by WinNonlin® software. Rats and mice appeared to be more effective at eliminating PFOS than monkeys. The serum elimination half-lives in the rodent species were on the order of 1–2 months; whereas, in monkeys, the serum elimination half lives approximated 4 months. Collectively, these studies provide valuable insight for human health risk assessment regarding the potential for accumulation of body burden in humans on repeated exposure to PFOS and PFOS-generating materials.

1. Introduction

Perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$) is a stable surfactant that has been used in harsh environments such as fire-fighting foams and acid mist suppression. PFOS can also occur from hydrolysis of perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$), and environmental or metabolic degradation of perfluorooctanesulfonamide (PFOSA, $C_8F_{17}SO_2NH_2$) and certain N-alkyl-perfluorooctanesulfonamides ($C_8F_{17}SO_2N(R)$) which are precursors used in various commercial and consumer application technologies [1–3]. PFOS was discovered to be widely distributed in biomonitoring samples from the human general population and wildlife [4,5].

The major manufacturer of these compounds in the past, 3M Company, phased out production between 2000 and 2002. PFOS since has been established as a persistent organic pollutant (POP) by the Stockholm Convention [6], and the production and use of PFOS and precursor materials which may generate PFOS has been restricted in many countries. Since *ca.* 2000, numerous biomonitoring studies have been conducted that consistently identify PFOS, as well as certain other perfluoroalkyls, with PFOS typically having the highest concentration [7–9]. Biomonitoring studies that allow observations over time suggest that measures taken to reduce the production and use of PFOS and precursor compounds since *ca.* 2000 have been effective in reducing general population blood concentrations of PFOS [10–13]. Cross sectional studies with American Red Cross adult blood donors suggested that there was an approximately 60% reduction in general population blood concentrations of PFOS between 2000–2001 and 2006 [13]. Recent general population serum PFOS concentration data from the United States Centers for Disease Control National Health And Nutrition Examination Survey (CDC NHANES) of 2007–2008 [14] also suggests an approximately 50–60% decline in serum PFOS concentration in the US general population when compared to the CDC NHANES data from 1999 to 2000 [15]. The observed declines in serum PFOS are consistent with a significant reduction in exposure [16]. The rate of decrease of PFOS concentration observed in the general population since *ca.* 2000 is consistent with the reported estimates of human half-life of serum PFOS elimination, with a geometric mean of 4.8 years (95% CI, 4.0–5.8) among 26 retired fluorochemical production workers [17].

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There have been few previously published pharmacokinetic studies for PFOS. In addition to the human elimination kinetics published by Olsen et al. [17], the elimination of PFOS from the serum of male and female monkeys was estimated at 200 days [18]. Benskin et al. [19] and De Silva et al. [20] have examined pharmacokinetics of PFOS isomers in Sprague-Dawley rats. The serum elimination half-lives in Sprague-Dawley rats were reported to be isomer-specific, with the linear isomer, constituting greater than 70% of the product produced by electrochemical fluorination, having an elimination half-life of 33 days after a single oral dose of PFOS at 400 μg/kg in males [19] and 80 days after 12 weeks of PFOS dietary treatment at 425 ng/g in males and females [20]. However, these estimations were derived with limited follow-up periods (approximately 1 half-life only). The low elimination rate of PFOS observed in the species studied has been hypothesized to be governed by a saturable renal resorption process [21,22], however, to date, a complete pharmacokinetic evaluation has been lacking. Distribution studies have typically been limited to reports on blood-based media and liver; although, human milk has been studied [23] as well as evaluation of PFOS distribution in selected tissues in mice [24,25].

Herein, we report on a series of experiments to evaluate the elimination profiles and estimate pharmacokinetic parameters of PFOS in rats, mice, and monkeys after single oral or IV administration. In addition, we report on the distribution of PFOS in rats 1, 2, and 89 days following a single oral (days 1 and 2) or IV (day 89) dose of ^{14}C-PFOS.

2. Materials and methods

2.1. Materials

Radiolabeled potassium perfluorooctanesulfonate ($CF_3(CF_2)_6(^{14}CF_2)SO_3^-$ K^+, ^{14}C-K^+PFOS, >99% pure) and potassium perfluorooctanesulfonate (K^+PFOS, 86.9% purity) were supplied by the 3M Company (St. Paul, MN). The potassium salt of PFOS was used because perfluorooctanesulfonic acid is a strong "organic" acid with limited aqueous solubility, and because the vast majority of the toxicology studies that have been conducted with PFOS have utilized the potassium salt. Administered doses are for K^+PFOS; however, concentrations in serum, liver, urine and feces are reported as PFOS anion, and percent recoveries of administered dose in those matrices are corrected for the potassium salt and corresponding purity. Potassium perfluorooctanoate (K^+PFOA, >99% purity), used as an internal standard for analytical extractions in the IV pharmacokinetic study in cynomolgus monkeys, was supplied by 3M Company, St. Paul, MN. Stable-isotope-labeled $^{18}O_2$-PFOS ($CF_3(CF_2)_7S(^{18}O_2)O^-$) used as an internal standard for extractions in the rat and mouse studies was supplied by Research Triangle Institute (Research Triangle Park, NC, USA). All other chemicals used were reagent-grade.

The ^{14}C-radiolabeled potassium salt of perfluorooctanesulfonate ($C_7F_{15}(^{14}C)F_2SO_3^-K^+$) was synthesized as follows. Crude ^{14}C-labeled perfluorooctanesulfonyl fluoride (^{14}C-POSF, $C_7F_{15}(^{14}C)F_2SO_2F$) was obtained after the electrochemical fluorination of $C_7H_{15}(^{14}C)H_2SO_2F$ with HF. After filtering the crude preparation through glass wool and washing twice with cold saturated $KHCO_3$ and water, it was dried over silica gel and underwent fractional distillation. Fractions 11–16 were combined to give the desired product, $C_7F_{15}(^{14}C)F_2SO_2F$. The purity was 98.15% per gas chromatography analysis. To synthesize ^{14}C-radiolabeled potassium salt of perfluorooctanesulfonate ($C_7F_{15}(^{14}C)F_2SO_3^-K^+$), ^{14}C-labeled POSF ($C_7F_{15}(^{14}C)F_2SO_2F$, 27.0 g) was slowly added to a pre-heated (78–80 °C) 500-mL 3-necked round bottom reflux condenser containing water (31.1 g) and potassium hydroxide pellets (85% purity, 15.53 g). A white gummy mixture was formed and maintained between 80 and 83 °C during the addition of radioactive $C_7F_{15}(^{14}C)F_2SO_2F$, and the entire mixture was heated at 85 °C for additional 3 h upon the completion of addition. The gummy solid was broken into smaller pieces and 10.8 mL of water was added. The pH of the solution was approximately 13.5. The upper aqueous phase was removed via aspiration and the reaming solids were washed successively with 45–50 °C water followed by aspiration (~72 mL). After the last wash, isopropanol (19.15 g) and water (17.0 g) were added to the solid, and the mixture was heated at reflux temperature for 1 h during which all the solids freely dissolved. The mixture solution was evaporated and concentrated on a steam bath, dried at 60 °C for 3 h via vacuum desiccators, and triturated once with Freon 113 to remove small traces of silicon oil impurity used as stirrer lubricant. The dried product (27.8 g) was $C_7F_{15}(^{14}C)F_2SO_3^-K^+$. The radiochemical purity was determined to be >99% per thin-layer chromatography and column chromatography; and the specific activity was 0.459 ± 0.0080 μCi/mg.

2.2. Laboratory animals and husbandry

Male and female Sprague-Dawley (SD) rats and CD-1 mice (8–10 weeks old) were purchased from Charles River Laboratory (Wilmington, MA or Portage, MI). Except for jugular-cannulated rats, which were individually housed in wire-bottom cages, all rats and mice were group housed in solid-bottom cages or single housed when placed in wire-bottom metabolism cages for collection of urine and feces. Rat chow (Purina Lab Chow or Teklad Mouse/Rat Chow) and tap water were provided *ad libitum* throughout the study except when fasting was required. Environmental controls for the animal room were set to maintain a temperature of 72 ± 3 °F, humidity of 30–70%, a minimum of 10 exchanges of room air per hour and a 12-h light/dark cycle.

The three male and three female cynomolgus monkeys (*Macaca fascicularis*) designated for use in this study were selected from an in-house colony of monkeys that were housed at Southern Research Institute (Birmingham, AL) prior to use on this study. These monkeys were purchased from Charles Rivers BRF, Inc. (Houston, TX). With the exception of one male, these same monkeys previously were given single IV bolus doses of the potassium salts of perfluorobutanesulfonate (PFBS, 10 mg/kg), perfluorobutyrate (PFBA, 10 mg/kg), perfluorohexanoate (PFHxA, 10 mg/kg), perfluorooctanoate (PFOA, 10 mg/kg), and perfluorohexanesulfonate (PFHxS, 10 mg/kg). The studies with PFBA, PFBA, and PFOA have been previously published [26–28]. The study with PFHxS is included in this issue [29]. Certified, commercial, dry monkey chow #5048 (PMI Feeds, Inc., St. Louis, MO) was fed to the monkeys 2–3 times each day. The diet was supplemented with fresh fruit/treats several times each week. Tap water (Birmingham, Alabama public water supply) was available to the monkeys *ad libitum*. The monkeys were housed in a room that was maintained at a temperature of 68–70.3 °F and a relative humidity of 22.2–65.7%. An automatic timer was set to control the room lights which provided 12-h of light/dark cycle per day.

Studies were performed in facilities accredited by the Association for Assessment and for the Accreditation of Laboratory Animal Care International. All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee. Animal care and procedures followed guidelines as specified the U.S. Department of Health and Human Services Guide for the Care and the Use of Laboratory Animals [30].

2.3. Analytical methods

2.3.1. Radiolabel studies with ^{14}C-K^+PFOS in rats

For studies with ^{14}C-K^+PFOS, the dosing solution and samples collected were analyzed for ^{14}C activities using a Packard Model 3385 Tri-Carb liquid scintillation counter. Fecal samples and tissue organs (when applicable) were homogenized in water (1:9 w/w); and all samples were weighed, and combusted with a Packard Model 306 Oxidizer followed by radiometric analyses of ^{14}C activity.

2.3.2. Monkey IV pharmacokinetic study

For the cynomolgus monkey IV pharmacokinetic study, PFOS standards in serum and urine were prepared in ranges of 20–10,000 ng/mL and 10–500 ng/mL, respectively. Monkey serum or urine samples (0.5 mL) were fortified with an internal standard, perfluorooctanoate, followed by the addition of an ion-pairing reagent (tetrabutylammonium hydrogen sulfate) and carbonate/bicarbonate buffer and extraction with ethyl acetate. The ethyl acetate layer was removed by evaporation, and the resulting residue was reconstituted in mobile phase (95% methanol with 1.5% formic acid, 5% 5 mM ammonium acetate). After filtration through a 0.2 μm syringe, the samples were transferred to auto sampler vials and analyzed by LC-MS/MS using an Applied Biosystems-Sciex model API 3000 mass spectrometer (Applied Biosystems/MDS-Sciex Instrument Corporation, Foster City, CA). For PFOS, the parent negative ion was monitored at 499 atomic mass units (amu). For the internal standard PFOA, the negative ion was transitioned and monitored from 413 → 369 amu.

2.3.3. Pharmacokinetic studies in rats and mice with K^+PFOS

For studies with rats and mice using K^+PFOS, serum and urine samples were used as collected. Commercially-purchased newborn calf serum (Invitrogen, Carlsbad, CA, USA) was used as blank matrix for preparation of serum matrix standards. Liver, kidney, urine, and feces collected from naïve rats or mice, as appropriate, were used as blank matrix for preparation of matrix-specific standards. Liver or kidney samples were allowed to thaw, and approximately 0.2 g of liver or kidney was weighed and homogenized with deionized water in a clean polypropylene tube. The ratio between liver or kidney and water was 1:4 (w/w). After the primary homogenization step, the whole homogenate was further sonicated for 30 min. Fecal samples were allowed to thaw and then the entire fecal sample for each rat or mouse was weighed and homogenized with deionized water in a clean polypropylene tube. The ratio between feces and water was 1:3 (w/w). After the primary homogenization step, the whole homogenate was centrifuged at 2500 × *xg* for 20 min and the corresponding supernatant was referred to as fecal extract.

To prepare matrix-matched PFOS standard curves, a PFOS solution prepared in methanol was aliquoted volumetrically to clean polypropylene tubes followed by addition of 100 μL of the appropriate blank matrix (serum, urine, liver, kidney, or fecal extract) to each tube. The matrix-matched standard curves for PFOS ranged from 1 to 1000 ng/mL.

Table 1
Summary of designs for pharmacokinetic studies in rats.

Section	Rat pharmacokinetic study	Subjects (n and sex)	K^+PFOS dose (mg/kg)	Dosing route(s)	Follow-up duration	Endpoint(s) evaluated
2.4.1	Pharmacokinetic and tissue distribution	n = 3/sex/time point	4.2[a]	Oral	1–144 h	^{14}C activities for plasma and tissues
2.4.2	Excretion and tissue distribution	n = 6 males	4.2[a]	IV	64–89 days	^{14}C activities for urine, feces, tissues, and plasma
2.4.3	Pharmacokinetic	n = 3/sex (IV); n = 3/sex (oral)	2; 2	IV; oral	24 h	Serum [PFOS] by LC-MS/MS
2.4.4	Serum uptake and urinary and fecal elimination	n = 3/sex (2 mg/kg); n = 5/sex (15 mg/kg)	2; 15	Oral; Oral	10–12 weeks	Serum, liver, urine, and feces [PFOS] by LC-MS/MS
2.4.5	Serum and liver elimination	n = 5 females/time point	15	Oral	1–35 days	Serum and liver [PFOS] by LC-MS/MS

[a] Administered as ^{14}C-K^+PFOS.

Details for solid phase extractions and LC-MS/MS conditions have been described previously [31–33]. Briefly, the solid-phase extraction (SPE) method used Oasis® HLB cartridges (Waters Corporation, Milford, MA, USA) and used $^{18}O_2$-PFOS as an internal standard. The method utilized an Applied Biosystems-Sciex model API 4000 mass spectrometer (Applied Biosystems/MDS-Sciex Instrument Corporation, Foster City, CA). PFOS ion transitions monitored were 499 → 80 amu for PFOS anion and 503 → 84 amu for the $^{18}O_2$-PFOS internal standard.

2.4. Rats

A series of studies was conducted in male and female Sprague-Dawley rats to characterize the pharmacokinetic profiles of PFOS. Table 1 summarizes these study designs.

2.4.1. Pharmacokinetic and tissue distribution of ^{14}C-K^+PFOS following a single oral dose

In order to understand the elimination profile of PFOS after a single oral dose as well as develop some understanding of tissue distribution of PFOS, male Sprague-Dawley rats (n = 24) were given a single oral dose of 4.2 mg/kg body weight of ^{14}C-K^+PFOS prepared in 0.9% NaCl. Immediately after dosing, subsets of rats were placed in metabolism cages, and urine and fecal samples were collected for 24 and 48 h post-dose (n = 3/time point). At designated periods (1, 2, 6, 12, 24, 48, 96, and 144 h post-dose), groups of rat (n = 3) were euthanized via diethyl ether anesthesia and blood samples (collected via descending aorta) were collected to obtain plasma. Both red blood cells and plasma samples were analyzed for ^{14}C activity. In addition, at 24 and 48 h post-dose, cumulative urine and fecal samples, spleen, digestive tract (esophagus, stomach, small intestine, large intestine, and colon), and the remaining carcass were analyzed for ^{14}C activities.

2.4.2. Excretion and tissue distribution of ^{14}C-K^+PFOS following a single IV dose

In order to understand the urinary and fecal elimination profile of PFOS after a single IV dose as well as develop some understanding of tissue distribution of PFOS after 89 days post-dose, male Sprague-Dawley rats (n = 6) were given a single IV dose of 4.2 mg/kg body weight of ^{14}C-K^+PFOS prepared in 0.9% NaCl via the tail vein. Urine and feces were collected at various intervals continuously for 89 and 64 days, respectively. At 89 days post-dose, rats were euthanized via diethyl ether anesthesia. Blood samples (red blood cells and plasma) and various whole organs (spleen, liver, brain, testes, adrenals, kidneys, lungs, and eyes) were collected in addition to partial samples from bone marrow (obtained from four major bones of the rear legs), skin, thigh muscles, subcutaneous fat, and abdominal fat. With the exception of carcass, all the harvested samples were analyzed for ^{14}C activity.

2.4.3. IV and oral pharmacokinetics of PFOS in jugular-cannulated rats after a single dose of K^+PFOS

In order to establish classical pharmacokinetic parameters related to absorption, distribution, and elimination, male and female Sprague-Dawley jugular-cannulated rats (n = 3/sex/dose group) were administered a single dose of 2 mg K^+PFOS/kg body weight either by tail-vein IV injection or by oral gavage. K^+PFOS solution was prepared in saline (for IV study) or distilled water (for oral gavage). Interim blood samples (approximately ~0.5 mL) were collected from cannula to obtain serum at 0.25, 0.5, 1, 2, 4, 8, 18, and 24 h post-dose. Serum samples stored at −80 °C pending analysis for PFOS by LC-MS/MS as previously described.

2.4.4. Serum uptake and urinary and fecal elimination of PFOS 10–12 weeks after a single oral dose of K^+PFOS

In order to better understand potential dose effects on uptake and elimination, to establish more precise elimination rates and characterize serum, urine, and fecal elimination, male and female Sprague-Dawley rats (n = 3–5/sex/dose group) were given a single oral dose of either 2 or 15 mg K^+PFOS/kg body weight. The K^+ PFOS solution was prepared in vehicle (0.5% Tween 20). Periodic interim serum (obtained from tail vein bleeding), urine, and fecal samples were collected throughout the study for at least 10 weeks post-dose. At study termination, rats were euthanized via CO_2 asphyxiation, blood (collected via abdominal aorta) and liver samples were harvested. All samples taken, including serum, urine, feces, and liver, were frozen with liquid nitrogen and stored at −80 °C pending analysis for PFOS by LC-MS/MS as previously described.

2.4.5. Serum and liver elimination of PFOS after a single oral dose of K^+PFOS

In order to study partitioning in serum and liver over an extended period after a single oral dose, female Sprague-Dawley rats (n = 5/time point) were given a single oral dose of 15 mg K^+PFOS/kg body weight. The K^+PFOS solution was prepared in vehicle (0.5% Tween 20). At designated time (days 1, 4, 7, 17, 28, and 35 post-dose), rats were euthanized via CO_2 asphyxiation, serum (processed from blood collected via abdominal aorta) and liver samples were harvested, frozen with liquid nitrogen, and stored at −80 °C pending analysis for PFOS by LC-MS/MS as previously described.

2.5. Serum uptake and urinary and fecal elimination in mice

In order to understand potential dose effects on kinetic parameters and to establish the distribution and elimination profiles of PFOS in serum, liver, kidney, urine, and feces over an extended time period following a single oral dose, male and female CD-1 mice were given a single oral dose of either 1 or 20 mg K^+PFOS/kg body weight. The K^+PFOS solution was prepared in vehicle (0.5% Tween 20). At designated times (2, 4, and 8 h post-dose and days 1 (24 h), 8, 15, 22, 36, 50, 64, and 141 post-dose), groups of mice (n = 4/sex/dose group) were euthanized via CO_2 asphyxiation. Blood (collected via abdominal aorta and processed to serum), kidneys, and liver samples were harvested. In addition, 24-h urine and feces were collected from mice prior to the day of necropsy. Serum samples were obtained after blood clotting and centrifugation (2000 × g, 15 min). All samples taken, including serum, urine, feces, kidneys, and liver, were frozen with liquid nitrogen and stored at −80 °C pending analysis for PFOS by LC-MS/MS.

2.6. IV pharmacokinetic study in cynomolgus monkeys

To establish classic pharmacokinetic parameters in a non-human primate species, male and female cynomolgus monkeys were given a single IV dose of K^+PFOS and serum and urine PFOS concentrations were observed for an extended time period. K^+PFOS was dissolved in sterile saline, USP (Phoenix Pharmaceutical Company, St. Joseph, MO; Lot 8101069) at 1 mg/mL. The formulation was stored refrigerated and used for dosing within 3 days after preparation; it was considered to be stable during this period. Dosing solution concentration and homogeneity analyses were not performed.

On Day 0, each of the three male and three female cynomolgus monkeys received a single IV dose of K^+PFOS at 2 mg/kg into a superficial arm or leg vein. Doses were administered at a volume of 2 mL/kg based on the Day 0 body weights. All monkeys were observed twice daily for clinical signs. Each monkey was weighed on Days 0, 4, 7, 14, 21, 28, 42, 56, 70, 85, 105, 126, and 151. Urine was collected in standard metabolism cages for 24-h intervals on the following days: prior to dose administration (Day -3; baseline), on Day 1 (0–24 h post-dose), on Day 2 (24–48 h post-dose), and on Days 7, 15, 21, 28, 42, 56, 70, and 91. The volume of each urine sample was measured. Urine samples were stored frozen (approximately −20 °C). Fecal samples were also collected but were not analyzed. Blood samples (2 mL) were collected at time 0 (pre-dose); 0.5, 2, 4, 8, 24, and 48 h; and subsequently on Days 4, 7, 14, 21, 28, 42, 56, 70, 105, and 161 post-dose. Samples were collected into tubes without anticoagulant and were allowed to clot at room temperature. The blood samples were then centrifuged, and the serum separated and stored at −20 °C until analyzed.

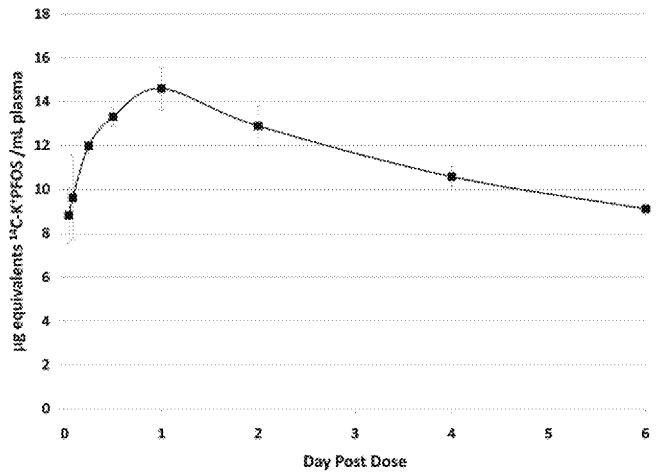

Fig. 1. Mean µg equivalents ^{14}C-K$^+$PFOS/mL plasma activity over time in male Sprague-Dawley rats (N = 3/time point) following a single oral dose of 4.2 mg ^{14}C-K$^+$PFOS/kg body weight. Error bars represent standard error.

2.7. Pharmacokinetic data analysis

Selected pharmacokinetic parameters were calculated from the serum PFOS concentration versus time data using WinNonlin® software (Pharsight Corp.; Mountain View, CA). Data obtained after IV or oral dosing were fit to a non-compartmental model. Statistically significant ($p < 0.05$) differences in the sex-specific arithmetic means for each pharmacokinetic parameter were determined by the Student's t-test when applicable. Mean values and standard errors (SE) for each parameter were calculated, except in the case of the mouse study, in which the mean by sex for each group of mice at each time point was used. When available, data for the fecal and/or urinary excretion of PFOS were expressed as a percent of the administered dose eliminated during the collection period. Liver PFOS concentrations, when available, were expressed as the mean ± SE concentration by sex and group. Statistically significant ($p < 0.05$) differences in the sex-specific arithmetic means for each pharmacokinetic parameter were determined by the Student's t-test.

3. Results

3.1. Rats

3.1.1. Pharmacokinetic and tissue distribution of ^{14}C-K$^+$PFOS following a single oral dose

Mean (±SE) µg equivalents ^{14}C-PFOS/mL in rat plasma after a single oral dose of 4.2 mg ^{14}C-K$^+$PFOS/kg body weight are illustrated in Fig. 1, and estimated pharmacokinetic parameters are shown in Table 2. The highest mean concentration in plasma measured was at 24 h post-dose (14.56 ± 0.97 µg equivalents/mL) and declined to 9.11 ± 0.24 µg/mL by 144 h post-dose. The plasma ^{14}C-PFOS elimination half-life was estimated to be 8.23 ± 1.53 days. In the group sacrificed at 24 h post-dose, approximately 99% of the given dose was recovered, with approximately 3% recovered in urine and feces (Table 3). In the group sacrificed at 48 h post-dose, approximately 117% of the given dose was recovered, with approximately 6% recovered in urine and feces (Table 3). The distribution pattern was very similar between the groups sacrificed at 24 and 48 h post-dose.

Table 2
Mean ± SE values for pharmacokinetic parameters in male Sprague-Dawley rats given a single oral dose of ^{14}C-K$^+$PFOS at 4.2 mg/kg and followed up for 144 h.

Parameter	
T_{max} (day)	1.00 ± 0.00
C_{max} (µg/mL)[a]	14.56 ± 0.97
Serum $[PFOS]_{last}$ (µg/mL)[a]	9.11 ± 0.24
λ (1/day)	0.0904 ± 0.0148
$T_{1/2}$ (days)	8.23 ± 1.53
CL (mL/day/kg)	24.15 ± 2.41
AUC (µg day/mL)	177 ± 18
Vd (mL/kg)	275 ± 22

[a] Expressed as µg equivalents ^{14}C-K$^+$PFOS/mL plasma.

Table 3
Mean % ^{14}C-K$^+$PFOS (± SE) recovered in urine, feces, and tissues in 24 and 48 h after a single oral dose of ^{14}C-K$^+$PFOS.

Compartment	% ^{14}C of dose recovered	
	0–24 h	0–48 h
Carcass	79.0 ± 1.8	94.2 ± 5.1
Digestive Tract plus contents	3.58 ± 0.23	3.32 ± 0.12
Feces	1.55 ± 0.15	3.24 ± 0.08
Urine	1.57 ± 0.25	2.52 ± 0.31
Plasma	11.02 ± 0.64 (estimated)[a]	10.01 ± 0.62 (estimated)[a]
RBC	2.29 ± 0.18 (estimated)[a]	3.25 ± 0.92 (estimated)[a]
Total	99.0	116.5

[a] A mean body weight of 300 g was used to estimate the RBC and plasma volume. Each rat was estimated to have 26.3 mL and 31.3 mL of RBC and plasma, respectively; therefore, the theoretical amount of ^{14}C-K$^+$PFOS administered was: 4.2 (mg/kg) × 0.3 (kg) × 1000 (µg/mg) = 1260 µg.

3.1.2. Excretion and tissue distribution of ^{14}C-K$^+$PFOS following a single IV dose

After a single IV dose of 4.2 mg ^{14}C-K$^+$PFOS/kg body weight to rats, mean (±SE) µg equivalents ^{14}C-PFOS/g (tissue or feces) or mL (plasma and urine) and the mean (±SE) µg equivalents of ^{14}C-PFOS expressed as % administered dose are presented in Table 4 for plasma, urine, feces, and several organs. Over an 89-day cumulative collection period, the mean percent of administered dose recovered in urine was 30.2 ± 0.6%. Feces collected for 64 days accounted for 12.6 ± 0.5% of the administered dose. Based on the average daily fecal excretion of ^{14}C over the last 28 days of collection, feces excreted between days 64 and 89 would be expected to contain 1–2% of the administer dose. On day 89 post-dose, only liver and plasma contained a substantial % of the administered dose (25.2 ± 1.2% and 2.81 ± 0.05%, respectively). Less than 0.5% of the administered ^{14}C-K$^+$PFOS dose was found in kidneys, lung, spleen, red blood cells, or testes. Concentrations of PFOS in bone marrow,

Table 4
Mean (± SE) ^{14}C-K$^+$PFOS concentrations and % dose (± SE) in rats 89 days after a single IV dose of 4.2 mg/kg ^{14}C-K$^+$PFOS.

Tissue/matrix	Mean concentration (µg/g or µg/mL)	% of total ^{14}C-K$^+$PFOS dose recovered in tissue/matrix
Urine (0–89 days)	NC[a]	30.2 ± 0.59
Feces (0–64 days)	NC[b]	12.6 ± 0.5
Liver	20.56 ± 0.84	25.2 ± 1.2
Plasma	2.21 ± 0.06	2.81 ± 0.05
Kidney	1.09 ± 0.05	0.27 ± 0.01
Lung	1.06 ± 0.06	0.13 ± 0.01
Spleen	0.51 ± 0.01	0.02 ± 0.002
RBC	0.45 ± 0.01	0.47 ± 0.04
Testes	0.36 ± 0.04	0.10 ± 0.004
Bone Marrow	0.46 ± 0.05	ND[c]
Adrenals	0.41 ± 0.01	ND
Skin	0.35 ± 0.03	ND
Muscle	0.29 ± 0.01	ND
Subcutaneous Fat	0.20 ± 0.07	ND
Eye	0.16 ± 0.03	ND
Abdominal Fat	≤0.08	ND
Brain	≤0.05	ND
Remaining carcass	–[d]	ND
Total	71.9	

[a] Not calculated, as collections were made over 89 days.
[b] Not calculated, as collections made over 64 days.
[c] Not determined, as either the whole tissue/matrix was not counted or there was difficulty in distinguishing between tissue/matrix concentration and blood/plasma within tissue.
[d] Remaining carcass was not counted.

Table 5
Mean ± SE values for pharmacokinetic parameters in jugular-cannulated Sprague-Dawley rats given either a single oral or a single IV dose of 2 mg K^+PFOS/kg body weight and followed up for 24 h.

Parameter	Sex	Oral	IV
T_{max} (day)	Male	0.25 ± 0.08	N/A[a]
	Female	0.03 ± 0.04	N/A
C_{max} (μg/mL)	Male	2.38 ± 0.19	3.33 ± 0.35
	Female	3.91 ± 0.10	3.38 ± 0.35
Serum $[PFOS]_{last}$ (μg/mL)	Male	1.89 ± 0.13	2.64 ± 0.33
	Female	2.73 ± 0.15	2.64 ± 0.18
λ (1/day)	Male	0.2232[b]	0.1768 ± 0.0804
	Female	0.3616 ± 0.0239	0.1224[b]
$T_{1/2}$ (days)	Male	3.10[b]	7.99 ± 4.94
	Female	1.94 ± 0.13	5.62[b]
CL (mL/day/kg)	Male	171[b]	118 ± 61
	Female	189 ± 19	72[b]
AUC (μg day/mL)	Male	11.70[b]	35.93 ± 21.67
	Female	10.80 ± 1.12	27.66[b]
Vd (mL/kg)	Male	765[b]	649 ± 51
	Female	521 ± 19	586[b]

[a] Not applicable.
[b] Parameters estimated was based on $N = 1$ rat.

adrenals, skin, muscle, subcutaneous fat, and eyes were less than 0.5 μg/g. The concentrations in brain and abdominal fat were not quantifiable. Only liver and plasma contained a substantial percentage of the dose at 89 days post-dose. In view of the relatively high ^{14}C content of plasma and red blood cells, the low level of radioactivity found for kidney, lung, testes, spleen, and other tissues is due in part to the blood that was contained within these tissue homogenates. Because ^{14}C activity from the remaining carcass was not determined, approximately 72% of the administered ^{14}C-K^+PFOS dose was accounted for among the matrices collected. With at least 43% recovered in urine and feces, this suggests that approximately 57% of the administered dose was still present in the body after 89 days, and roughly half of dose present in the body after 89 days was distributed to liver and plasma (approximately 25% and 3% of administered dose, respectively).

3.1.3. IV and oral pharmacokinetics of PFOS in jugular-cannulated rats after a single dose of K^+PFOS

Presented in Table 5 are the pharmacokinetic parameters calculated from serum concentrations of PFOS obtained from jugular-cannulated rats that received either a single IV or a single oral dose of 2 mg K^+PFOS/kg body weight. A non-compartmental model best fit the majority of the data.

For the IV study, although three female rats were dosed, serum values from two female rats did not fit the model due to lack of an observed elimination such that λ could not be estimated; hence, pharmacokinetic parameter estimation could not be obtained from these two female rats. Mean serum C_{max} values (expressed as mean ± SE) were similar between male and female rats (3.33 ± 0.35 μg/mL and 3.38 ± 0.35 μg/mL, respectively) and at 24 h post-dose, mean serum PFOS concentrations were also similar between males and females (2.64 ± 0.33 μg/mL and 2.64 ± 0.18 μg/mL, respectively). Based on the IV study, the mean serum elimination half-lives ($T_{1/2}$) were estimated to be 7.99 ± 4.94 days in males and 5.62 days based on data from one female rat, which were similar to the half-life of 8.23 days estimated from the ^{14}C-K^+PFOS study.

For the oral gavage study, although three male rats were dosed, serum values from two male rats did not fit the model due to lack of an observed elimination such that λ could not be estimated; hence, pharmacokinetic parameter estimation was obtained based on one male and three female rats. Mean T_{max} values were 0.25 ± 0.08 day and 0.03 ± 0.04 day for males and females, respectively, and mean C_{max} values were 2.38 ± 0.19 μg/mL and 3.91 ± 0.10 μg/mL, respectively. The mean serum PFOS concentrations at 24 h were statistically significantly lower in males (1.89 ± 0.13 μg/mL) than females (2.73 ± 0.15 μg/mL). Based on the oral study, the mean serum elimination half-lives ($T_{1/2}$) were estimated to be 3.10 days in males, based on data from one male rat, and 1.94 ± 0.13 days in females.

Table 6
Mean ± SE values for pharmacokinetic parameters in Sprague-Dawley rats given a single oral dose of K^+PFOS at 2 or 15 mg/kg and followed up for at least 10 weeks.

Parameter	Sex	2 mg/kg	15 mg/kg
T_{max} (day)[a]	Male	8.00 ± 0.00	1.00 ± 0.00
	Female	8.00 ± 0.00	0.84 ± 0.16
C_{max} (μg/mL)	Male	1.75 ± 0.08	41.84 ± 2.32
	Female	4.42 ± 0.15	39.46 ± 0.79
Serum $[PFOS]_{last}$ (μg/mL)	Male	0.48 ± 0.01[b]	4.60 ± 0.18[c]
	Female	2.07 ± 0.20[b]	14.66 ± 1.09[c]
Liver $[PFOS]_{last}$ (μg/g)	Male	8.58 ± 1.69[b]	25.82 ± 1.27[c]
	Female	5.48 ± 0.50[b]	27.64 ± 3.50[c]
% PFOS dosed in urine, 0–24 h	Male	0.12 ± 0.02	0.19 ± 0.03
	Female	0.45 ± 0.13	0.26 ± 0.03
λ (1/day)	Male	0.0184 ± 0.0015	0.0170 ± 0.0008
	Female	0.0111 ± 0.0004	0.0107 ± 0.0016
$T_{1/2}$ (days)	Male	38.31 ± 2.32	41.19 ± 2.01
	Female	62.30 ± 2.09	71.13 ± 11.25
CL (mL/day/kg)	Male	22.24 ± 0.28	11.28 ± 0.56
	Female	5.39 ± 0.20	4.88 ± 0.52
AUC (μg day/mL)	Male	90 ± 1	1342 ± 64
	Female	371 ± 14	3234 ± 381
Vd (mL/kg)	Male	1228 ± 97	666 ± 21
	Female	484 ± 24	468 ± 25

[a] T_{max} were likely overestimations within the limit of study design because samples were not collected immediately post-dose.
[b] Samples were obtained on Day 72 post-dose.
[c] Samples were obtained on Day 85 post-dose.

3.1.4. Serum uptake and urinary and fecal elimination of PFOS 10–12 weeks after a single oral dose of K^+PFOS

The mean ± SE for several pharmacokinetic parameters estimated from the oral uptake and elimination study in rats given either 2 or 15 mg K^+PFOS/kg body weight and followed up for at least 10 weeks are presented in Table 6. Also included in Table 6 are serum and liver PFOS concentrations upon terminal sacrifice.

As illustrated in Fig. 2, after a single oral dose at 2 mg/kg, mean C_{max} serum PFOS concentrations were lower in males (1.75 ± 0.08 μg/mL) than in females (4.42 ± 0.15 μg/mL). Mean λ for serum elimination of PFOS also were different between males and females (0.0184 ± 0.0015 $day^{-1}$and 0.0111 ± 0.0004 day^{-1}, respectively), resulting in mean $T_{1/2}$ values of 38.31 ± 2.32 days and 62.30 ± 0.20 days, respectively. Upon study termination (72 days post-dose), the respective mean serum PFOS concentrations in males and females were 0.48 ± 0.01 μg/mL and 2.07 ± 0.20 μg/mL, and the respective mean liver PFOS concentrations in matched males and females were 8.58 ± 1.69 μg/g and 5.48 ± 0.50 μg/g.

As illustrated in Fig. 3, after a single oral at 15 mg/kg, mean C_{max} serum PFOS concentrations were similar in males (41.84 ± 2.32 μg/mL) and females (39.46 ± 0.79 μg/mL). Similar to the parameters obtained with 2 mg/kg dose, mean λ for serum elimination of PFOS were still different between males and females (0.0170 ± 0.0008 $day^{-1}$and 0.0107 ± 0.0016 day^{-1}, respectively), resulting in mean $T_{1/2}$ values of 41.19 ± 2.01 days

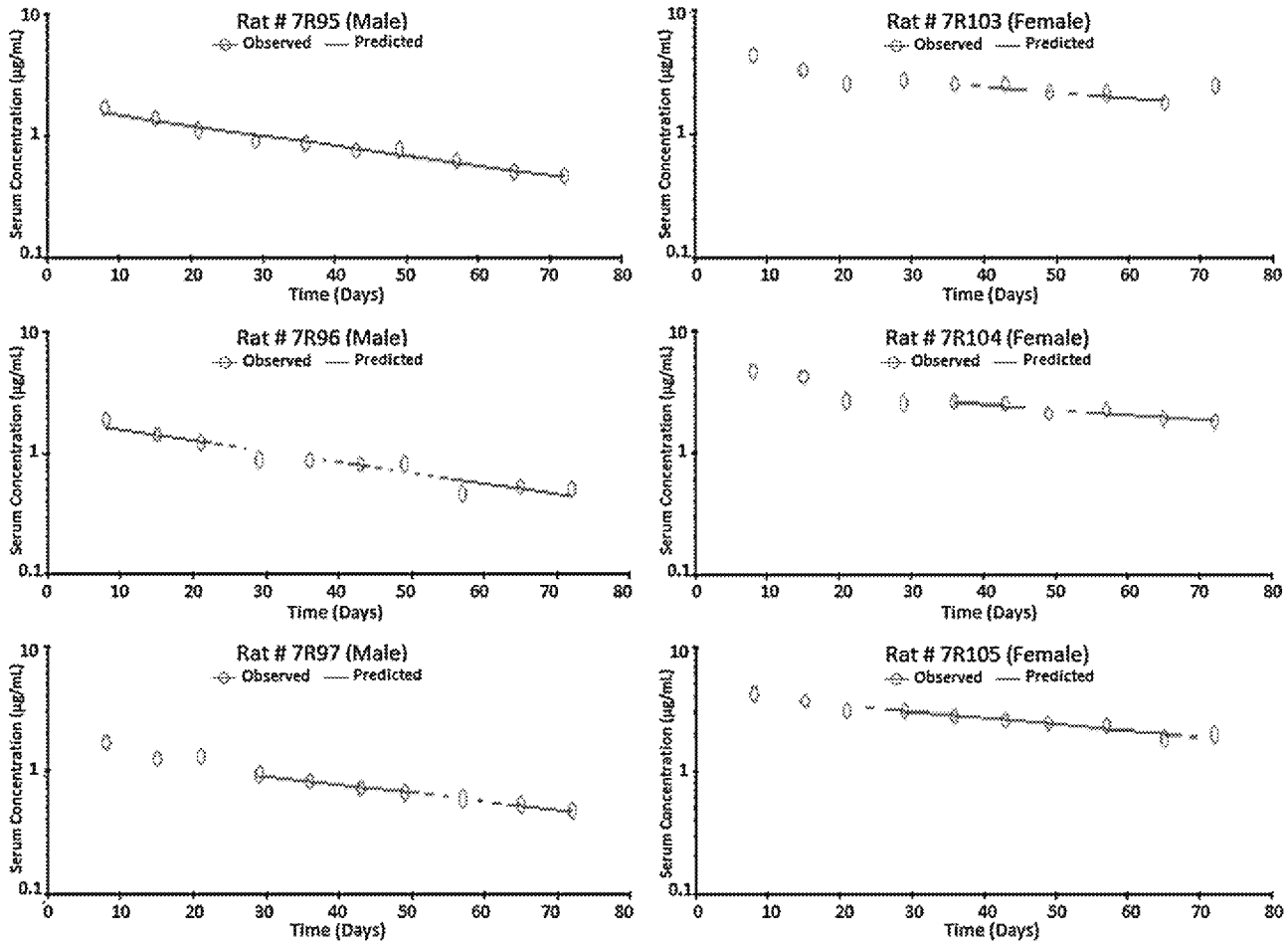

Fig. 2. Serum PFOS concentrations (µg/mL) in male (left column) and female (right column) Sprague-Dawley rats ($N = 3$/sex) over time after a single oral dose of 2 mg K^+PFOS/kg body weight.

and 71.13 ± 11.25 days, respectively. Upon study termination (85 days post-dose), the respective mean serum PFOS concentrations in males and females were 4.60 ± 0.18 µg/mL and 14.66 ± 1.09 µg/mL, and the respective mean liver PFOS concentrations in matched males and females were 25.82 ± 1.27 µg/g and 27.64 ± 3.50 µg/g.

At both study doses, mean PFOS concentrations in liver were higher than the paired serum PFOS concentrations. Mean Vd were in approximately the same range. Differences in λ not only corresponded to statistically significantly different serum elimination half-lives between male and female rats, but also reflected statistically significantly different clearance rates (CL) and AUC.

The percent of administered PFOS dose excreted during overnight urine and fecal collections are shown in Figs. 4 and 5, respectively. For PFOS analyses on feces obtained from 2 mg/kg dose group rats, all samples were <LLOQ (40 ng/g) and are not shown in Fig. 5. While PFOS was slowly excreted both in urine and feces, the urinary route was dominant in terms of percent of dose excreted.

3.1.5. Serum and liver elimination of PFOS after a single oral dose of K^+PFOS

To evaluate the partitioning in serum and liver over an extended period after a single PFOS administration, paired serum and liver concentration data obtained over a 35-day period following a single oral dose of 15 mg/kg K^+PFOS are presented in Fig. 6. Mean time group liver PFOS concentrations were significantly higher than the paired serum PFOS concentrations at all time points; however, the ratio of liver to serum PFOS concentration remained roughly the same at all time points. Maximum measured serum and liver PFOS concentrations were obtained on day 4 post-dose (51.18 ± 6.71 µg/mL and 78.96 ± 16.09 µg/g, respectively).

3.2. Mice

Table 7 provides the several pharmacokinetic parameters estimated in male and female mice from data obtained after single oral doses of 1 or 20 mg K^+PFOS/kg body weight. By dose groups, mean PFOS concentrations for serum, kidneys, and liver are presented in Fig. 7 (1 mg/kg K^+PFOS) and Fig. 8 (20 mg/kg K^+PFOS). Mean PFOS concentrations were highest in liver followed by serum and then kidney. Regardless of dose, mean serum elimination $T_{1/2}$ values were quite similar between male and female mice (42.81 days versus 37.80 days at 1 mg/kg and 36.42 days versus 30.45 days at 20 mg/kg for males and females, respectively) (Table 7). During the study, less than 0.7% of the administered PFOS dose was recovered in the urine and feces at any given 24-h sample collection period (Figs. 9 and 10). There was no clear indication of a sex-related difference. Although lower than the Vd values obtained in rats, Vd estimates in mice were still in a range consistent with a predominant extracellular distribution.

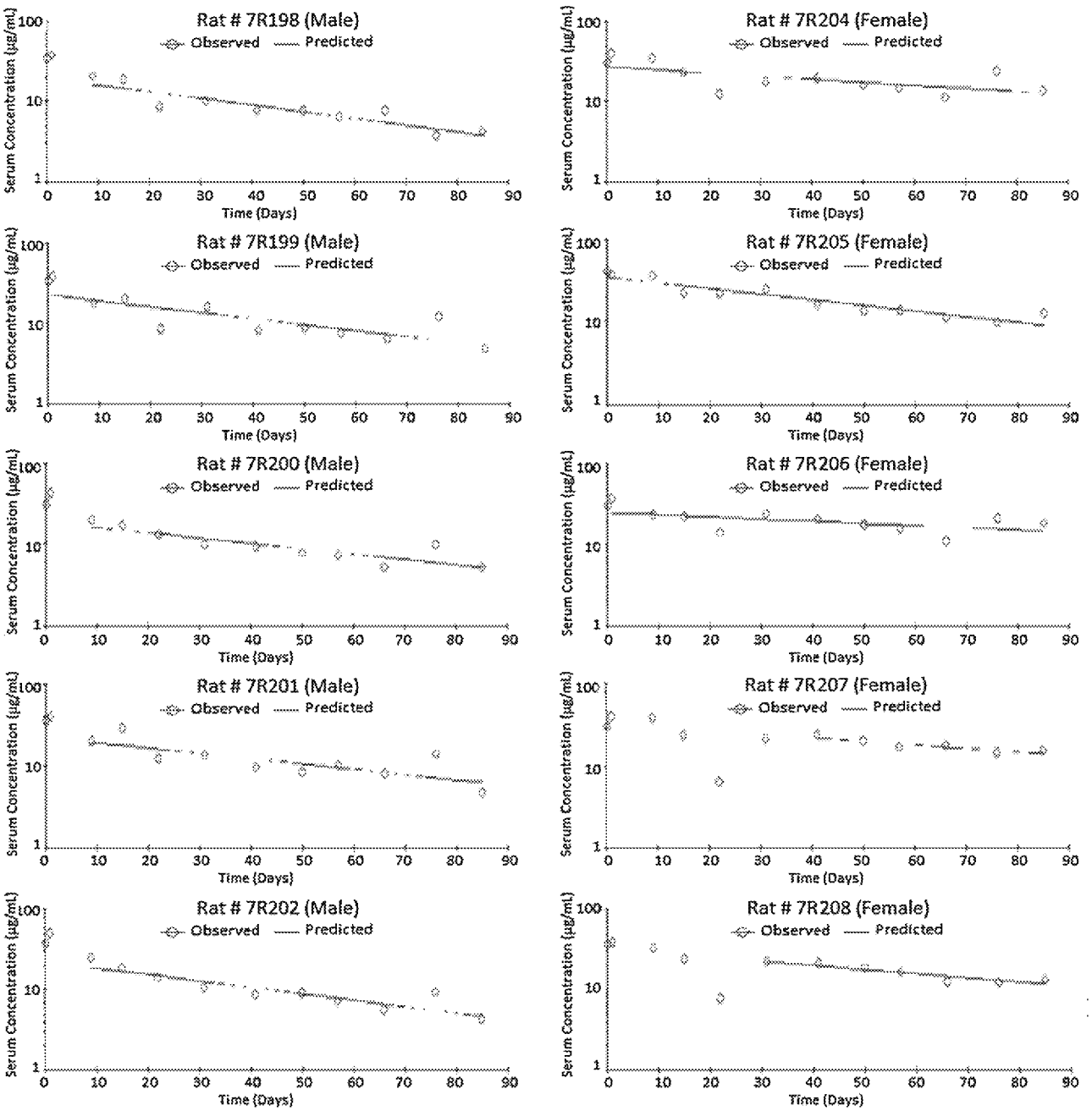

Fig. 3. Serum PFOS concentrations (μg/mL) in male (left column) and female (right column) Sprague-Dawley rats ($N = 5$/sex) over time after a single oral dose of 15 mg K^+PFOS/kg body weight.

3.3. Monkeys

Presented in Table 8 are pharmacokinetic parameters in cynomolgus monkeys upon the administration of a single IV dose of 2 mg/kg K^+PFOS. Mean serum concentrations at 24 h for males and females were 8.31 ± 0.72 μg/mL and 6.17 ± 1.13 μg/mL, respectively. PFOS was still quantifiable in serum at Day 161 (3.82 ± 0.01 μg/mL and 2.46 ± 0.23 μg/mL in males and females, respectively). For all monkeys, low levels (0.06–0.18%) of the administered PFOS dose were consistently recovered in the urine during any given 24-h period of sample collection in the study with no clear indication of a sex-related difference in the urinary excretion of PFOS. Concentration-versus-time data were best fit to a non-compartmental model (Fig. 11). Mean serum elimination half-lives for PFOS in the male and female monkeys were 131 ± 7 days and 110 ± 15 days, respectively. The mean value for CL was statistically significantly higher in females than males. Similar to rats and mice, the mean Vd suggested predominantly extracellular distribution.

4. Discussion

The results from this series of studies have established pharmacokinetic parameters of PFOS for the rat, mouse, and monkey. A feature of the studies reported herein is that, in addition to providing classical pharmacokinetic parameters from short-term studies, elimination of PFOS has been studied over extended time periods. Elimination of PFOS from the serum of retired, occupationally-exposed humans over a period of several years has previously been studied [17]. The present work provides a perspective on species

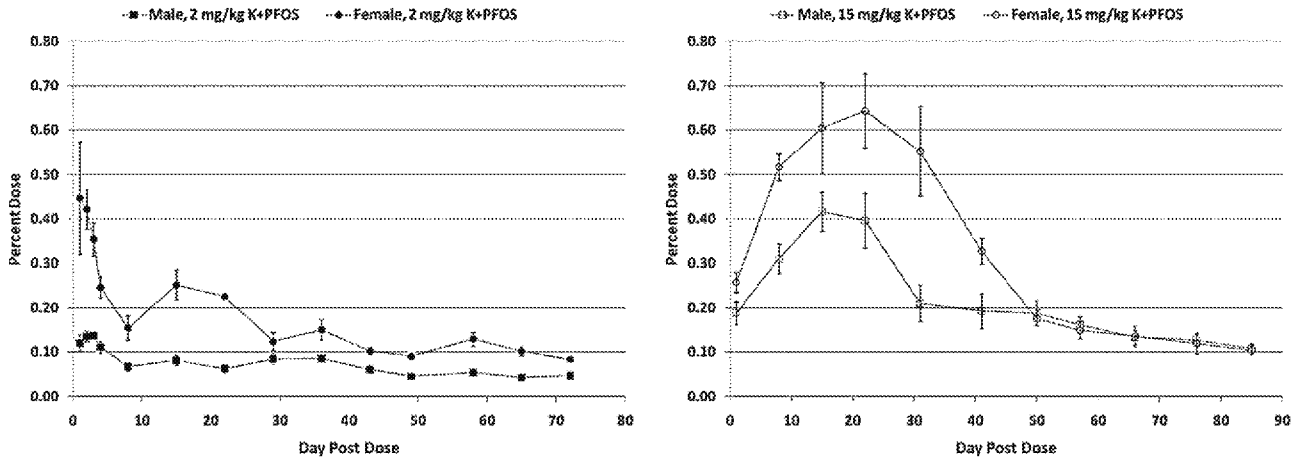

Fig. 4. Mean percent (%) PFOS dose eliminated in urine in male and female Sprague-Dawley rats at various time after a single oral dose of either 2 or 15 mg K^+PFOS/kg body weight. Each data point represents a 24-h collection period. Solid squares and solid circles represent male and female rats given 2 mg K^+PFOS/kg body weight (N = 3/sex) while open squares and open circles represent male and female rats given 15 mg K^+PFOS/kg body weight (N = 5/sex). Error bars represent standard error.

Table 7
Pharmacokinetic parameters in CD-1 mice given a single oral dose of K^+PFOS at 1 or 20 mg/kg and followed for 20 weeks (141 days).

Parameter	Sex	1 mg/kg	20 mg/kg
T_{max} (day)	Male	2	0.33
	Female	0.33	0.33
C_{max} (μg/mL)	Male	4.938	72.53
	Female	4.938	77.50
Serum $[PFOS]_{last}$ (μg/mL)	Male	0.344	5.15
	Female	0.276	3.47
% PFOS dosed in urine, 0–24 h	Male	0.52 ± 0.09	0.36 ± 0.09
	Female	0.42 ± 0.16	0.25 ± 0.08
λ (1/day)	Male	0.0162	0.0190
	Female	0.0183	0.0228
$T_{1/2}$ (days)	Male	42.81	36.42
	Female	37.80	30.45
CL (mL/day/kg)	Male	4.70	5.00
	Female	4.74	5.95
AUC (μg day/mL)	Male	212	4000
	Female	210	3363
Vd (mL/kg)	Male	290	263
	Female	258	261

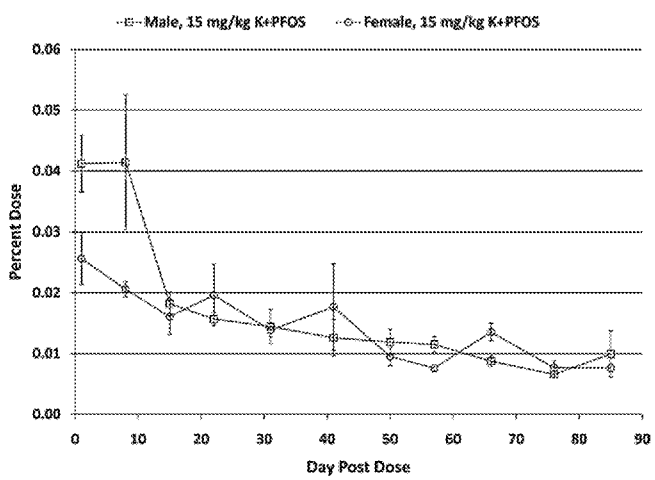

Fig. 5. Mean percent (%) PFOS dose eliminated in feces in male (open squares) and female (open circles) Sprague-Dawley rats (N = 5/sex) at various time after a single oral dose of 15 mg K^+PFOS/kg body weight. Each data point represents a 24-h collection period. Error bars represent standard error.

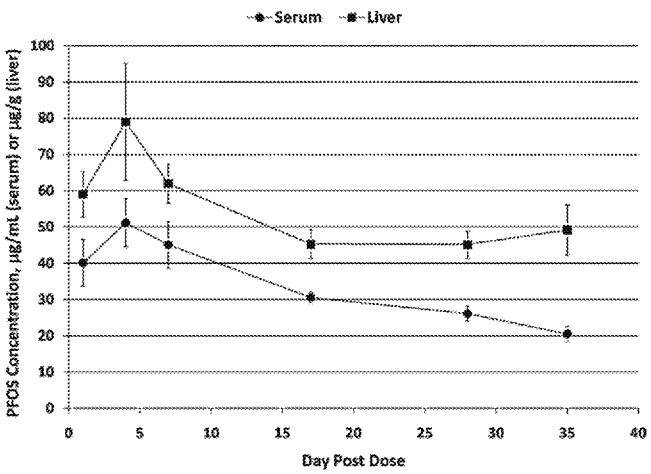

Fig. 6. Mean serum and liver PFOS concentrations in μg/mL (serum) or μg/g (liver) for female Sprague-Dawley rats (N = 5/time point) over 35 days following a single oral dose of 15 mg K^+PFOS/kg body weight. Error bars represent standard error.

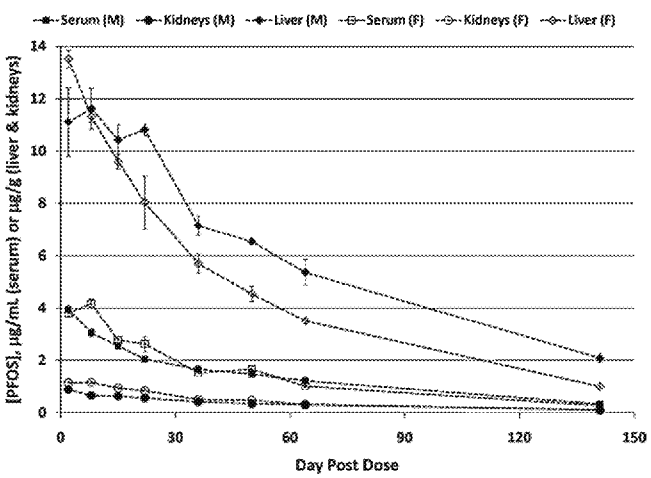

Fig. 7. Mean serum, kidney, and liver PFOS concentrations in μg/mL (serum) or μg/g (kidney and liver) for male and female CD-1 mice (N = 4/sex/time point) over 141 days following a single oral dose of 1 mg K^+PFOS/kg body weight. Male mouse data for serum, kidney, and liver are illustrated with solid squares, circles, and diamonds, respectively. Female mouse data for serum, kidney, and liver are illustrated with open squares, circles, and diamonds, respectively. Error bars represent standard error.

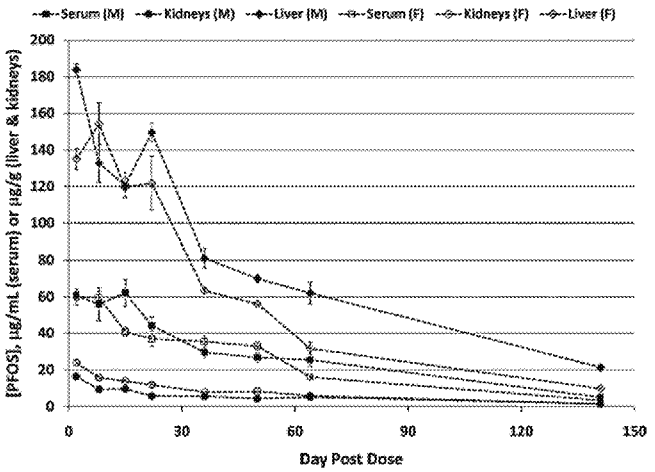

Fig. 8. Mean serum, kidney, and liver PFOS concentrations in µg/mL (serum) or µg/g (kidney and liver) for male and female CD-1 mice ($N = 4$/sex/time point) over 141 days following a single oral dose of 20 mg K^+PFOS/kg body weight. Male mouse data for serum, kidney, and liver are illustrated with solid squares, circles, and diamonds, respectively. Female mouse data for serum, kidney, and liver are illustrated with open squares, circles, and diamonds, respectively. Error bars represent standard error.

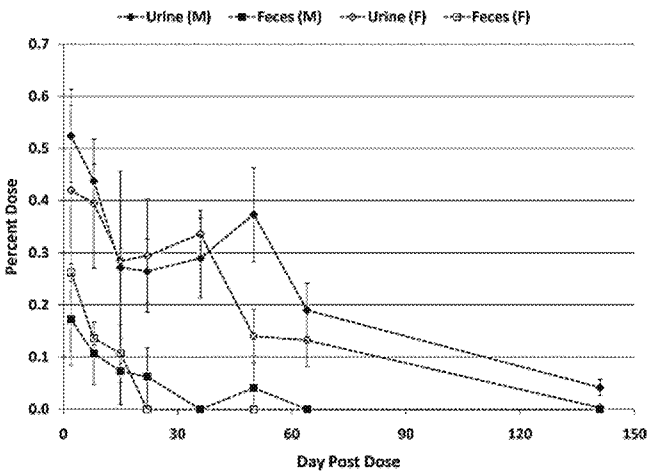

Fig. 9. Mean percent (%) PFOS dose eliminated in urine and feces in male and female CD-1 mice ($N = 4$/sex/time point) over 141 days following a single oral dose of 1 mg K^+PFOS/kg body weight. Male mouse data for urine and feces are illustrated with solid diamond and squares, respectively. Female mouse data for urine and feces are illustrated with open diamond and squares, respectively. Error bars represent standard error.

differences in elimination that is of value in evaluating the results of toxicological and epidemiological studies for human health risk assessment. In the case of PFOS, the large differences in elimination kinetics between rodent species, cynomolgus monkeys, and

Table 8
Mean ± SE values for pharmacokinetic parameters in cynomologus monkeys given a single IV dose of K^+PFOS at 2 mg/kg and followed up for 161 days.

Parameter	Male	Female
Serum $[PFOS]_{0.5\,h}$ (µg/mL)	15.05 ± 0.71	10.14 ± 1.17
Serum $[PFOS]_{24\,h}$ (µg/mL)	8.31 ± 0.72	6.17 ± 1.13[a]
Serum $[PFOS]_{day\ 161}$ (µg/mL)	3.82 ± 0.01	2.46 ± 0.23
% dose in urine, 0–24 h	0.064 ± 0.004	0.056 ± 0.015
C_{max} (µg/mL)	16.37 ± 1.05	11.50 ± 0.68
$T_{1/2}$ (days)	132 ± 7	110 ± 15
CL (mL/day/kg)	1.10 ± 0.06	1.65 ± 0.04
AUC (µg day/mL)	1792 ± 64	1126 ± 99
Vd (mL/kg)	202 ± 13	274 ± 28

[a] Based on $N = 2$ serum samples only; the last sample had insufficient volume.

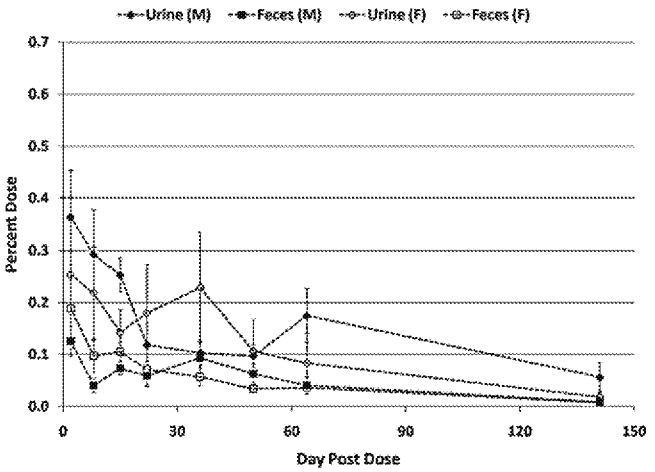

Fig. 10. Mean percent (%) PFOS dose eliminated in urine and feces in male and female CD-1 mice ($N = 4$/sex/time point) over 141 days following a single oral dose of 20 mg K^+PFOS/kg body weight. Male mouse data for urine and feces are illustrated with solid diamond and squares, respectively. Female mouse data for urine and feces are illustrated with open diamond and squares, respectively. Error bars represent standard error.

humans bring into question the adequacy of standard human health risk assessment practices that are principally based on externally administered dose. Not only are PFOS elimination rates vastly different between rodent species, monkeys, and humans, but also distribution of PFOS to liver, a key target of PFOS, differs significantly between rodent species and primates. It is clear that the pharmacokinetic differences between the species used to develop the toxicological profiles of PFOS and humans must factor into the extrapolation of results from toxicological studies to human risk of exposure to PFOS at occupational or general environmental levels. To that end, the combined studies reported herein provide a firm and comprehensive basis for understanding differences between species and developing risk assessment methodology that incorporates adjustment for pharmacokinetic differences.

The dose levels administered were not designed to represent general environmental exposures. The doses administered were designed to be in a range consistent with doses delivered in toxicological studies or achieving serum concentrations experienced from occupational exposures. Thus the 2 mg/kg IV dose administered to cynomolgus monkeys achieved initial serum PFOS concentrations that were at the high end of occupationally exposed worker serum PFOS concentrations.

With the exception of one male monkey, the monkeys used in the present study had also been used previously to study the pharmacokinetics of perfluorobutanesulfonate, perfluorobutyrate, perfluorohexanoate, perfluorooctanoate, and perfluorohexanesulfonate. These prior studies were conducted over an approximately 15-month period (from April 10, 2000 until July 29, 2001). Based on last drawn serum concentrations (<5 ng/mL) and the serum elimination half-lives determined for PFBS [25], PFBA [24], and PFHxA (1.5 and 0.8 days for males and females, respectively, unpublished) and the time elapsed between the last serum sample for these three compounds and the date of dosing for PFOS on July 30, 2001, no interference would be expected between these three compounds and PFOS. Considering the serum PFOA elimination half-lives determined for males and females [26] and the period of nearly six months between the last draw for PFOA, which revealed that the males were at or approaching the method LLOQ (20 ng/mL) and the females averaged approximately 3000 ng/mL, serum PFOA concentrations would be expected to be in the low ng/mL range and, therefore, would not be expected to interfere with the kinetics of PFOS. For PFHxS, the last serum draw occurred one day before injection of PFOS, and the six monkeys had a serum PFHxS

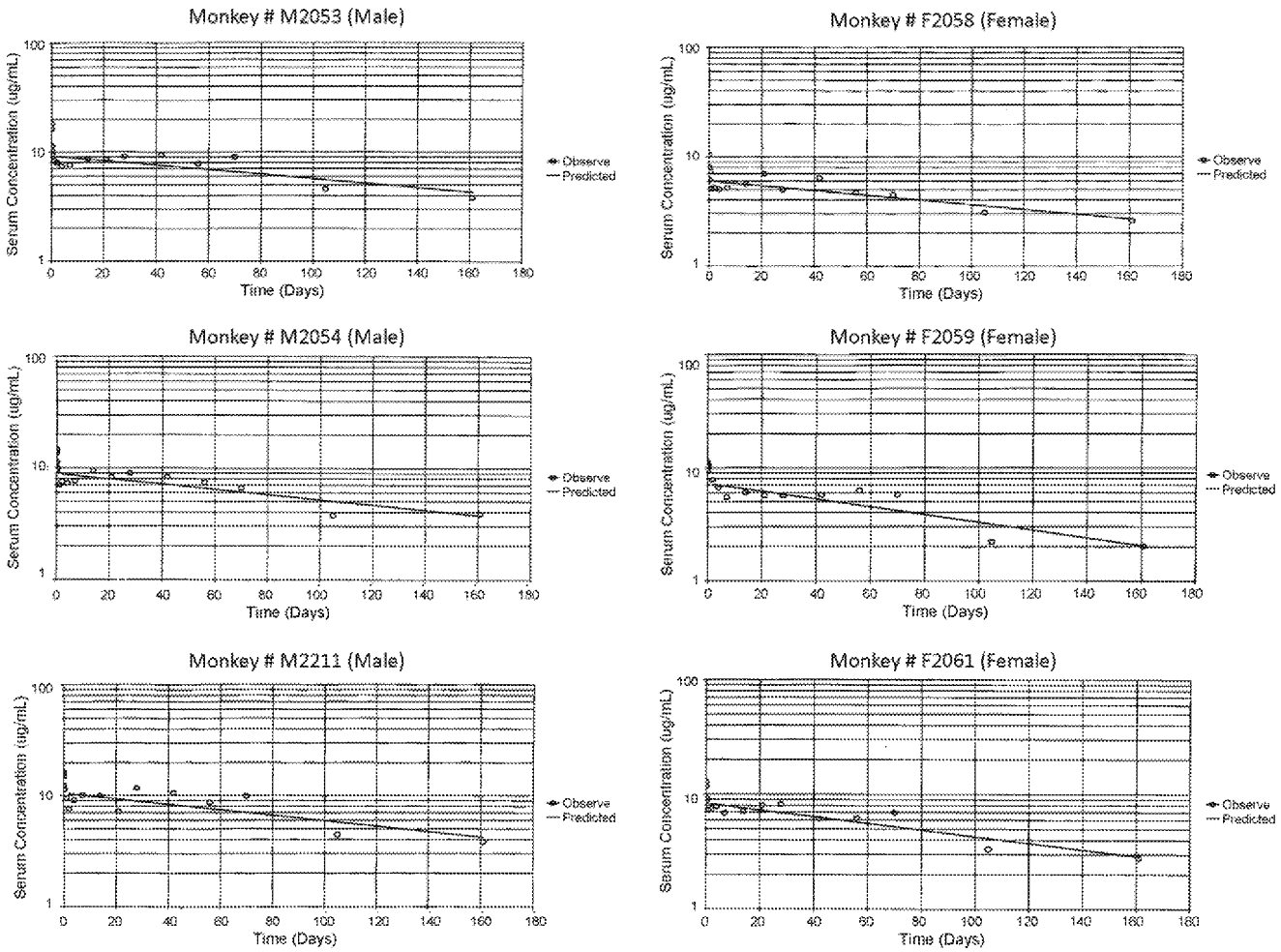

Fig. 11. Serum PFOS concentrations (μg/mL) in male (left column) and female (right column) cynomologus monkeys ($N = 3$/sex) over time after a single IV dose of 2 mg K^+PFOS/kg body weight. Error bars represent standard error.

concentration of 14,520 ng/mL. The latter average serum PFHxS concentration is of the same approximate magnitude as the Cmax values reported below for PFOS. It is therefore possible that some interaction between PFHxS and PFOS kinetics may have occurred; however, the serum elimination half-life estimated for PFOS was consistent with that estimated for PFHxS and also consistent with that estimated by Seacat et al. [18] from a follow-up of monkeys given daily oral doses of potassium PFOS over a six-month period and followed in recovery for one year.

The principal differences observed between species in the pharmacokinetic parameters measured were in elimination rates. Rats and mice appeared to be more effective at eliminating PFOS than monkeys. The serum elimination half-lives in the rodent species followed over extended time periods (10–20 weeks) were on the order of 1–2 months; whereas, in monkeys, the serum elimination half lives approximated 4 months when studied over a 23-week period. Within the first 24-h after K^+PFOS administration, <0.7% of the administered PFOS dose was recovered in the urine in rats and mice. The urinary recovery was <0.07% in monkeys for the initial 24 h, consistent with the slower elimination observed in cynomolgus monkeys than in rodents.

In rats, a serum elimination half-life of 8.2 days was estimated by extrapolation based on uptake and elimination of a single oral dose of ^{14}C-K^+PFOS in male rats over a six-day period and was consistent with those for male rats derived from the short-term (24-h) IV and oral pharmacokinetic studies in jugular-cannulated rat studies as well (8 and 3 days, respectively). However, there were several instances in the latter study in which the elimination rate constant could not be estimated due to lack of elimination over the 24-h period, and, even when estimated, the elimination rates obtained may not be reliable due to the small fraction eliminated over the period. When post-dose follow up period was extended to at least 10 weeks, the serum PFOS elimination half-lives obtained for male rats after oral administration were approximately an order of magnitude higher. Following a single IV dose of ^{14}C-K^+PFOS, an average of 30.2% of ^{14}C-K^+PFOS was recovered in urine of male rats over 89 days and an average of 12.6% in feces over 64 days following a single IV dose of ^{14}C-K^+PFOS. Based on the average daily fecal excretion of ^{14}C-K^+PFOS over the last 28 days of collection, feces excreted between days 64 and 89 would be expected to contain an additional 1–2% of the delivered dose. Therefore, serum elimination $T_{1/2}$ for PFOS based on the shorter-term studies overestimates the rate of whole-body elimination. This overestimation in shorter-duration studies may be due to initial more rapid phase elimination of PFOS and/or redistribution within the body.

The studies reported herein and the repeat-dose studies of Seacat et al. [34] and Curran et al. [35] have noted significant uptake of PFOS in the liver of rats. Seacat et al. [34] reported mean group liver to serum PFOS concentration ratio ranging from 2.5:1 to 12.2:1, with a grand mean of 5.4:1. Curran et al. [35] reported mean group liver to serum PFOS concentration ratio ranging from 1.3:1 to 51.3:1, with a grand mean of 29.4:1. In male and female cynomologus monkeys, Seacat et al. [18] found that liver to serum PFOS concentration ratio ranged from 0.9:1 to 2.7:1. In humans, Olsen

et al. [36] reported that the liver to serum PFOS concentration ratio among 23 paired liver and serum donor samples ranged from 0.9:1 to 1.7:1 with a mean of 1.3:1.

In the studies reported herein, liver PFOS concentrations, when available, were always higher than serum PFOS concentrations for rats and mice. Individual rat liver to serum PFOS concentration ratios ranged from 1.0:1 to 3.4:1, with a mean of 1.7:1. Similarly, individual mouse liver to serum PFOS concentration ratios ranged from 1.7:1 to 6.2:1, with a mean of 3.3:1. The reason for the difference in rat liver to serum PFOS concentration ratios between the present study and those of Seacat et al. [34] and Curran et al. [35] is not currently understood. The Seacat et al. [34] and Curran et al. [35] studies were dietary studies of 4–14 weeks duration while the present study was a single dose gavage study. Johnson et al. [37] provided evidence for enterohepatic circulation of PFOS in male rats, which could be a factor in maintaining higher liver to serum PFOS concentration ratios on repeat dosing. In addition, it could be speculated that PFOS, which has been shown to activate xenosensor nuclear receptor peroxisome proliferator activated receptor α (PPARα) as well as constitutive androstane receptor (CAR) and pregnane X receptor (PXR) [38,39] under similar dosing conditions to those used by Seacat et al. and Curran et al., may change the expression of organic anion transporters capable of increasing liver uptake or decreasing liver efflux of PFOS. Han et al. [40] had provided evidence for the involvement of organic anion transporting polypeptides in the hepatocellular uptake of the PFOS congener, perfluorooctanoate. Recently, Bijland et al. [41] have found PFOS up-regulates genes involved in fatty acid uptake and transport in liver of ApoE*3-Leiden.CETP mice during dietary treatment for several weeks. To the extent that PFOS may utilize fatty acid transport systems, increased transporter-mediated hepatocellular uptake of PFOS may partially explain the basis for the increased liver to serum PFOS concentration ratio.

Volumes of distribution (Vd) estimated for the species studied (rats, mice, and monkeys) appeared to be similar. Although the Vd for rats in the IV and oral studies with non-radioactive K^+PFOS was approximately twice those obtained in the studies with mice and monkeys, the study in rats with ^{14}C-K^+PFOS yielded a Vd similar to those for mice and monkeys. Although the reason for higher values in the rat obtained with non-radiolabeled K^+PFOS remains recondite, based on review of all the data, it would be reasonable to conclude that the Vd in the three species studied likely is in the range of 200–300 mL/kg body weight. Thus, PFOS appears to be distributed predominantly in extracellular space.

In rats, sex differences in pharmacokinetics have been noted for perfluorobutyrate [26], perfluorohexanesulfonate [29], and PFOA (first observed by Griffith and Long [42] and reviewed by Kudo and Kawashima [43]). For PFOS, as reported herein, although major differences between sexes within species were not observed, it is also worth noting that female rats given a single oral dose of K^+PFOS appeared to maintain a higher body burden and somewhat lower rate of serum elimination than males. Indeed, when followed over a 10–12 week period following single oral doses of 2 or 15 mg/kg, the mean male serum PFOS elimination half-lives were approximately 60% of the mean female half-lives. This observation suggests a modest sex difference in serum PFOS elimination in rats after receiving oral doses. A similar observation was also reported during a developmental neurotoxicity study with K^+PFOS [33] in which serum PFOS concentration in male pups was similar to female pups on postnatal day 21 but it was 1/5–1/3 of female serum PFOS on postnatal day 72. The authors speculated that the difference in serum PFOS elimination was perhaps associated with sexual maturation between postnatal day 21–72, with males eliminating PFOS from serum at a somewhat higher rate. There was no apparent sex difference in serum elimination of PFOS in either mice or monkeys.

In the only human serum PFOS elimination study available to date reported by Olsen et al. [17], the geometric mean serum PFOS elimination half-life among 26 retired fluorochemical workers followed for approximately five years was estimated at 4.8 years days (95% CI, 4.0–5.8). This reported value is in stark contrast to the mean serum PFOS elimination half-life of 121 days observed among the three male and three female monkeys reported herein as well as the serum PFOS elimination values reported herein for rats and mice. Cross-sectional studies of general population serum PFOS concentrations over time have demonstrated that these concentrations have been declining since *ca.* 2000, when the major manufacturer of PFOS and substances that can degrade to PFOS initiated a two-year manufacturing phase-out [10–13], which resulted in decreased environmental releases [16]. The rate of decline of general population serum PFOS concentrations also is consistent with the geometric mean half-life estimated by Olsen et al. [17]. A similar decline since *ca.* 2000 also has been observed for PFOS concentrations in human milk from Stockholm, Sweden [23]. These additional observations support the serum PFOS elimination half-life value reported by Olsen et al. for humans [17].

Based on studies conducted with PFOA (a PFOS congener), it may be reasonable to speculate that the differences in PFOS elimination between species and the sex differences in PFOS elimination within species in rats could be due to differences in expression of organic anion transporters. Vanden Heuvel et al. [44] first noted that the male and female difference in urinary elimination of PFOA in rats was related to testosterone. Kudo et al. [45] further confirmed the role of testosterone in mediating the difference between male and female rats in urinary elimination of PFOA. The potential role of differential (by sex) expression of renal organic anion transporters in rats in the observed sex difference in renal excretion of PFOA was further established by Kudo et al. [46], including the possible role of apical expression of the uptake transporter, Oatp1, in renal proximal tubules of male rats in facilitating reabsorption of PFOA from the urinary filtrate. Hinderliter et al. [47] demonstrated that the ability of female rats to excrete PFOA in urine more rapidly than males develops concurrently with sexual maturation of females. Several recent studies have demonstrated that PFOA is a potential substrate for renal organic anion transporters in rats [48–50] and humans [51,52]. Analysis of the kinetic data from the single-dose IV study in monkeys with K^+PFOS reported herein as well as with K^+PFOA [28] in the same set of male and female cynomolgus monkeys (with the exception of one male) has suggested a potential role for saturable renal tubular reabsorption [21]. Andersen et al. [21] suggested that changing the transport maximum in a human pharmacokinetic model could account for the longer half-life of PFOS in humans as compared to monkeys. At this time, it is not known to what extent the kinetics of the perfluoroalkylsulfonates may be determined by organic anion transporter mediated processes and how these may differ between species and sex within species.

In discussing species differences in elimination of PFOS from serum, a consideration of differences in serum protein binding should not be overlooked. We have previously evaluated the binding of PFOS to rat, monkey, and human plasma using ultrafiltration techniques [53]. At 100,000 ng/mL concentration of PFOS in plasma, 99.7, 99.9, and 99.9 percent of the PFOS remained bound to the plasma of rats, monkeys, and humans, respectively. These differences would not be expected to contribute to the differences in elimination rates observed among these species.

In summary, the pharmacokinetic profile of PFOS was evaluated for multiple species, including rat, mouse, and monkey. There were variations observed in the serum elimination half-lives of PFOS across the three species with sex-specific elimination differences likely in the rat but not demonstrated in mice or monkeys. Collectively, these studies provide valuable insight for human health risk

assessment regarding the potential for accumulation of body burden in humans on repeated exposure to PFOS-generating materials.

Conflict of interest

Shu-Ching Chang, David Ehresman, Sheila Gibson, Jill Hart, and John Butenhoff are employees of the 3M Company, a former manufacturer of PFOS and related materials. Patricia Noker (current active employee) and Gregory Gorman (former employee) of Southern Research Institute were contracted by 3M Company to conduct the IV pharmacokinetic study in monkeys. Major funding for the study was from 3M Company.

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